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BRIEF COMMUNICATION

Alcohol Intake Is Inversely Related to Plasma Renin Activity in the Genetically Selected Alcohol-Preferring and -Nonpreferring Lines of Rats

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GRUPP, L. A., H. KALANT AND F. H. H. LEENEN. *Alcohol intake is inversely related to plasma renin activity in the genetically selected alcohol-preferring and -nonpreferring lines of rats.* PHARMACOL BIOCHEM BEHAV **32**(4) 1061–1063, 1989.—Studies involving both animals and humans strongly suggest that alcoholism is, in part, genetically determined. One approach to studying this genetic component is to determine whether rats, genetically selected to prefer (P line) or avoid (NP line) alcohol, show differences in those physiological systems which modulate alcohol intake. It has previously been shown that alcohol intake in randomly bred stock rats is sensitive to and inversely related to manipulations which alter activity in the renin-angiotensin (R-A) system. In the present report the basal level of activity in the R-A systems of the P and NP rats as measured by plasma renin activity (PRA) was first assessed following which continuous access to alcohol (10% v/v) and water was offered for a period of five days. PRA was found to be inversely related to the amount of alcohol that was consumed. The P rats drank significantly larger amounts of alcohol than the NP rats who basically avoided the drug. The P rats had a significantly lower PRA than the NP rats. It is suggested that the genetic selection that favored different levels of alcohol consumption in the P and NP rats may have brought about this effect through differences in the activity of the renin-angiotensin systems in the two lines.

Plasma renin activity Alcohol consumption Alcohol-preferring and -nonpreferring rats Renin-angiotensin system

THE identification of biological factors underlying excessive alcohol use and the development of pharmacological interventions for treating human alcoholism would be facilitated by the availability of an animal model of alcoholism. Randomly bred stock rats do not normally ingest excessive quantities of alcohol voluntarily, and while a number of methods can be used to encourage intake (e.g., fluid deprivation or fluid adulteration, food deprivation, or schedule-induced polydipsia), the use of these procedures violates the criterion of an animal model which stipulates that the oral intake be voluntary (12). As an alternative, selectively bred lines of rats have been developed which either shun or seek out and voluntarily consume excessive amounts of alcohol. Although there are a number of such lines of rats [e.g., UchB and UchA (16); AA and ANA (1)], the current focus of attention is on the P (alcohol-preferring) and NP (alcohol-nonpreferring) lines primarily because they are the best characterized and appear to satisfy most of the criteria for an animal model of alcoholism (13).

Over the past several years, research in our laboratory with randomly bred Wistar stock has demonstrated that manipulations that alter activity in the renin-angiotensin (R-A) system can produce profound changes in voluntary alcohol intake. For example, administration of a low salt diet together with the diuretic furosemide (9); the serotonin uptake inhibitor, fluoxetine (8); the octapeptide, angiotensin II (3,7); the surgical production of

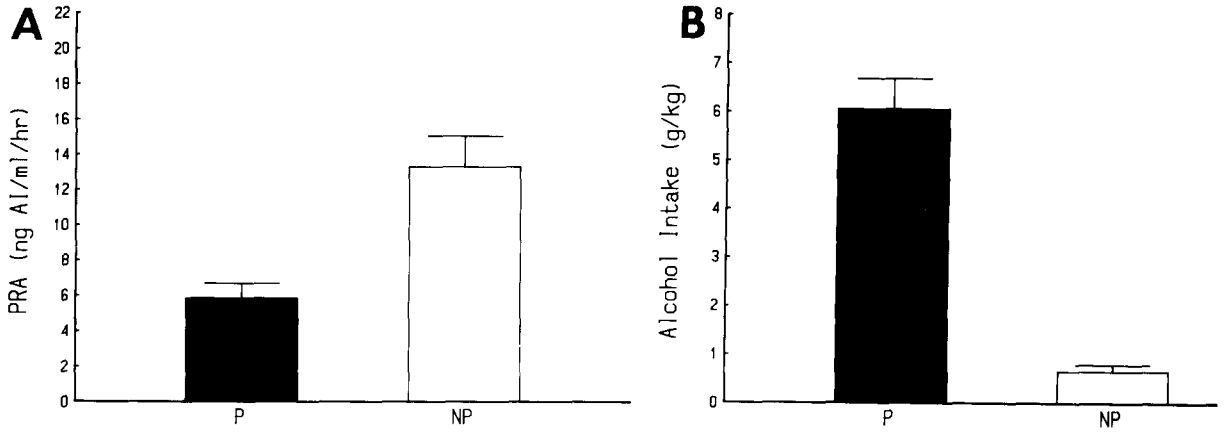

FIG. 1. (A) Mean plasma renin activity (PRA) in the alcohol-preferring (P) and alcohol-nonpreferring (NP) rats determined prior to the access to alcohol. Bars represent the standard error of the mean. (B) Mean daily alcohol (10% v/v) intake across the five days of continuous 24-hr access to both alcohol and tap water. Bars represent the standard error of the mean.

hypertension by unilateral renal artery stenosis (4,5); and, under certain conditions, even the angiotensin I converting enzyme inhibitors (21), all elevate R-A activity and all decrease alcohol intake. Conversely, rats on a high salt diet (6); the salt-sensitive Dahl line of hypertensive rats (10); and rats with lesions to the angiotensin-receptor-rich area postrema in the medulla (22,23), all have decreases in the R-A system and all have elevated alcohol intake. This list of diverse manipulations, all of which share the common property of being able to alter R-A activity, has led to the suggestion that the R-A system may be a common path through which alcohol consumption is regulated (2). We now report that the alcohol-preferring P rats have a significantly lower level of R-A activity than their nonpreferring NP counterparts, suggesting that the R-A system may also be implicated in the expression of differences in alcohol drinking between these two genetically selected lines of rats.

METHOD

Seven female P and 7 female NP rats, obtained from the colony at the Indiana University School of Medicine, were individually housed in a temperature-controlled environment on a 12-hr light/dark cycle with lights on at 7:00 a.m. The animals had continuous access to food and water in their home cage, except where otherwise noted, and weighed 275–375 g at the beginning of the experiment. All were from the 27th generation except 3 P rats which were from the 28th generation and one NP rat which was from the 26th generation.

First, plasma renin activity (PRA) was measured in both P and NP rats in blood samples obtained from the tail, by means of an antibody trapping technique followed by radioimmunoassay for angiotensin I (20). All samples were obtained on a single day. Next, in order to confirm that there was indeed a group difference in the consummatory drive for alcohol, both the P and NP rats were allowed free access to two tubes, one containing 10% v/v alcohol made up in tap water and the other containing only tap water for a period of five days. Pelleted rat chow was available ad lib, and the positions of the two tubes were alternated daily. Consumption of alcohol and water was measured over consecutive 24-hr periods.

RESULTS

Figure 1A compares the mean PRA in both the P and NP rats. It can be seen that PRA, which is an index of activity in the R-A system, was significantly lower in the P rats than in the NP rats, $t(12)=3.8$, $p=0.001$. Figure 1B shows that the P rats indeed preferred alcohol and consumed an average 6 g/kg/day (75.7 ml/kg/day) across the five-day period, while the NP rats avoided alcohol and consumed an average of only 0.7 g/kg/day (8.2 ml/kg/day), $t(12)=8.3$, $p<0.00001$. Average water consumption of the NP rats was significantly higher than that of the P rats [68 ml/kg/day vs. 15 ml/kg/day; $t(12)=7.1$, $p<0.0001$]. The mean preference ratio (daily volume of ethanol solution to daily volume of water consumed) was 5:1 for the P rats and 0.12:1 for the NP rats. These results are in good agreement with published data on consumption levels and preference for P and NP rats (15).

DISCUSSION

The heuristic promise afforded by genetically selected lines of rats such as the P and NP lines is that of identifying differences in biological systems that might be directly related to the polar differences in the avidity of these lines for consuming alcohol. One difference already identified between the two lines is in the serotonin system—the P rat has lower serotonin content than the NP rat in a variety of different brain areas (17–19). The present report showing an inverse relationship between PRA and voluntary alcohol intake in the two lines of rats draws attention to the R-A system as a possible mediator of the differences in their alcohol intake. The fact that the serotonin system is known to modulate the R-A system (14, 24, 25), together with a recent report showing that the reduction in alcohol intake by serotonin uptake inhibitors appears to be mediated through the R-A system (8), strongly suggest that the differences between the two lines in the serotonin and the R-A systems might be different manifestations of the same basic phenomenon. Interestingly, a previous study had already hinted that genetic selection procedures could influence both voluntary alcohol intake and the R-A system (10). In that study, the Dahl lines of salt sensitive (SS) and salt resistant (SR) rats were of specific interest because the SS rat was known to have lower PRA than the SR rat (11). Using the same two-bottle 24-hr choice procedure employed in the present experiment, we found that the SS rat, genetically selected to develop hypertension, drank 4.8 g/kg/day of a 6% (v/v) alcohol solution while the SR rat consumed only 2.9 g/kg/day (10). The amount consumed by the SS rat in that study is comparable to the average intake of the alcohol-preferring P line of rat.

The fact that the R-A system which is known to produce changes in alcohol intake of randomly bred Wistar stock (2–10, 22, 23), is also the system which, in the present study, showed a marked difference in activity in the P and NP lines (originally derived from Wistar stock) suggests that genetic selection may have produced contrasting levels of alcohol intake in these lines by enhancing a difference in activity in their R-A systems. These considerations, in turn, raise the more general question of the role of the R-A system in the etiology of alcoholism.

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